Conferences and Reviews

Differential Diagnoses of Bone Marrow Granuloma

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The finding of a granuloma on a bone marrow biopsy is not common. The etiologic spectrum encompasses a wide variety of disorders. We present the case of a young woman with a bone marrow granuloma and discuss the differential diagnosis, emphasizing the most common causes. This disorder can be associated with serious diseases.

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Bone marrow granuloma is not a frequent finding in a bone marrow biopsy. The incidence ranges from 0.3% to 2.2%, depending on the series.[1-5] A large number of cases was first published in 1950.[3] Many diseases have been implicated in the formation of granulomas in the bone marrow, but they are not specific and do not usually show characteristic features that typify a specific diagnosis. We report the case of a young woman with fever, anemia, and a bone marrow granuloma. We review the differential diagnosis and the literature, including five major studies of bone marrow granuloma.

Report of a Case

The patient, a 19-year-old woman, was seen because of fever and shortness of breath on exertion. These symptoms had been present for a week before admission. She had no other symptoms. Her history was relevant only for a cholecystectomy at age 16. She said she did not use tobacco, alcohol, or drugs of abuse and was taking acetaminophen for her fever.

On physical examination, the patient was obese but in no distress. Her blood pressure was 130/75 mm of mercury, pulse rate 100 beats per minute, and temperature 39.5°C (103°F). She had no palpable cervical lymph nodes, and no other abnormalities were noted.

Laboratory test results are shown in Table 1. Her chest x-ray film was unremarkable: no infiltrate, effusions, hilar abnormalities, or other findings were noted. A computed tomographic (CT) scan of the chest showed no abnormalities. A CT scan of the abdomen showed mild splenomegaly and multiple enlarged lymph nodes in the periaortic area. A skin test for *Candida* species, mumps, and purified-protein derivative showed anergy.

During the initial evaluation, a lymphoma was strongly suspected. A bone marrow biopsy specimen showed only a noncaseating granuloma without any signs of lymphoma (Figures 1 and 2). Despite stains for acid-fast bacilli (AFB), fungus, Gram's stains, immunophenotyping, and several histologic studies, no definitive diagnosis could be established. Tests for antibodies to the human immunodeficiency virus (HIV) were negative, as were those for cytomegalovirus, *Histoplasma capsulatum*, and *Brucella* species. A sputum specimen did not show any mycobacteria.

The patient underwent exploratory laparotomy with diagnostic splenectomy and multiple biopsies. All showed noncaseating granulomas. An angiotensin-converting enzyme (ACE) level was elevated. Empirical therapy for tuberculosis with isoniazid and rifampin was initiated while culture results were pending. There was no improvement with this treatment after two weeks. No bone marrow, liver, lymph node, or spleen specimen grew any pathogen after eight weeks. The final diagnosis of sarcoidosis was made. A trial of steroid therapy was successful, and the patient was doing well two months after discharge from the hospital.

Discussion

Many disorders have been implicated in the pathogenesis of bone marrow granuloma. They encompass many unrelated diseases including malignant lesions; viral, bacterial, and fungal infections; autoimmune diseases; drugs; and sarcoidosis. Although some specific pathologic findings can point toward certain diagnoses—for instance, caseation in tuberculosis, Reed-Sternberg cells in Hodgkin's lymphoma, poorly organized granulomas in HIV infection—these findings are uncommonly seen in the marrow. Frequently the diagnosis cannot be made solely on pathologic criteria. Rather, it will have to be based on epidemiologic, clinical, laboratory, and radiologic data.

Tables 2 and 3 list the most frequent causes of bone marrow granuloma in five studies.[1-5]

Malignant neoplasms have been reported as the cause of bone marrow granulomas in 20% to 25% of the cases,

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CT = computed tomographic
EBV = Epstein-Barr virus
HIV = human immunodeficiency virus

most being malignant lymphomas of the Hodgkin's and non-Hodgkin's type, the Hodgkin's type being more frequent.[1-5] A bone marrow granuloma occurring in patients with Hodgkin's disease is uncommon.[6-8] An incidence of bone marrow granuloma of 5% has been reported in patients with known Hodgkin's lymphoma.[8] The finding of a Reed-Sternberg cell within the granuloma is rare.[2,3,6]

A bone marrow granuloma in patients with lymphoma can be due to the invasion of the bone marrow or, more frequently, a nonspecific immunologic change due to cancer. Its presence has been associated with a good prognosis in patients with Hodgkin's disease.[6,9]

Granulomas associated with a good prognosis have been described to be composed of groups of epithelioid histiocytes with occasional giant cells and no Reed-Sternberg cells. They are commonly distributed in a paravascular location. They cannot be considered evidence of invasion of the bone marrow.[6] A distinction should be made between epithelioid granulomas and lipogranulomas, frequently seen after lymphangiography in patients with Hodgkin's disease and carrying no prognostic importance.[10]

Distinguishing between sarcoidosis and Hodgkin's disease granuloma can be difficult if based on pathologic criteria only. Some authors are reporting an increased incidence of Hodgkin's disease in patients with sarcoidosis. The coexistence of both is possible. The following criteria are suggested for the diagnosis of duality: a biopsy obtained from an unrelated site, with clinical, radiologic, and biologic correlation.[11]

In general, it is rare for a non-Hodgkin's lymphoma to present initially as a bone marrow granuloma. In one study, 10 of 372 patients with known non-Hodgkin's lymphoma (2.7%) had bone marrow granulomas.[12] In non-Hodgkin's lymphoma, especially with follicular small cleaved cells, mixed small cleaved cells, and large cells, granulomatous lesions are sometimes observed. Such lesions consist of a large cell center surrounded by small cells and clusters of epithelialized histiocytes, giving the appearance of a granuloma. Distinguishing this lesion from a true epithelioid granuloma can be difficult. Immunophenotyping can be helpful in such cases.[13]

Many other malignant neoplasms have been associated with bone marrow granulomas.[1-3,9,14,15] The diagnosis is usually easily made in these cases, as the cancer is usually in an advanced stage.

Infectious causes occupy a major place in the differential diagnosis of bone marrow granulomas. Bacterial, viral, fungal, and parasitic infections have been reported. Brucellosis is a frequent and well-established cause. The incidence of brucellosis ranged between 0% and 12.5%,[1-4] and bone marrow granulomas were found in 28% to 68% of cases.[16,17] Granulomas consist of epithelialized cells surrounded by lymphocytes, plasmocytes, and occasional Langhans' cells.[3] Cytophagocytosis was commonly seen, but caseating necrosis is absent.[16] Serologic tests and bone marrow cultures are usually positive (86% and 92%, respectively).[18]

Typhoid fever is another common cause of bone marrow granuloma. In a study in Spain, the incidence of typhoid fever was 10%.[4] Chronic granulomatous inflammation was the most common finding on bone marrow biopsies and was associated with hemophagocytosis.[19] Bone marrow cultures were more sensitive than blood cultures for organism recovery.[20]

Many authors have reported Q fever to be a classic cause of bone marrow granulomas.[21] In a report of seven bone marrow biopsies in patients with Q fever, all seven had a granuloma.[22] Five showed nonspecific findings,

TABLE 1.—*Laboratory Test Results on a Young Woman With Unexplained Fever*

Test	*Result, SI Units (Conventional)*
Hemoglobin, grams/liter (grams/dl)	80 (8.0)
Hematocrit, fraction of 1 (%)	0.24 (24)
MCV, fl (μm^3)	85 (85)
Leukocyte count, $\times 10^9$/liter (cells/mm^3)	6 (6,000)
Platelet count, $\times 10^9$/liter (/mm^3)	450 (450,000)
Electrolytes	Normal
BUN and creatinine	Normal
Iron, μmol/liter (μg/dl)*	6 (32)
Total iron-binding capacity, μmol per liter (μg/dl)†	43 (241)
Ferritin, μg/liter (ng/ml)‡	150 (150)
Reticulocyte count, fraction of 1 (%)	0.01 (1)
Haptoglobin, grams/liter (mg/dl)§	1.48 (148)
Vitamin B_{12}, pmol/liter (pg/ml)‖	830 (1,130)
Erythrocyte folate, nmol/liter (ng/ml)¶	1,790 (790)
ESR, mm/hour	>100 mm/sec
Alkaline phosphatase, U/liter#	500
AST (SGPT), U/liter**	50
ALT (SGOT), U/liter††	40
ACE level, $nmol \cdot liter^{-1} \cdot sec^{-1}$ (nmol/ml/min)‡‡	1,630 (98)
Antinuclear and anti-DNA antibody tests	Negative
Rheumatoid factor	Negative
Coombs' direct and indirect	Negative
Ham test	Negative

ACE = angiotensin-converting enzyme, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, MCV = mean corpuscular volume, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, SI = Système International

*Normal, 7 to 27 μmol/liter (40 to 150 μg/dl).
†Normal, 39 to 72 μmol/liter (220 to 400 μg/dl).
‡Normal, 10 to 107 μg/liter (10 to 107 ng/ml).
§Normal, 0.13 to 1.63 grams/liter (13 to 163 mg/dl).
‖Normal, 162 to 693 pmol/liter (220 to 940 pg/ml).
¶Normal, 280 to 1,360 nmol/liter (125 to 600 ng/ml).
#Normal, 15 to 110 U/liter.
**Normal, 0 to 45 U/liter.
††Normal, <670 $nmol \cdot liter^{-1} \cdot sec^{-1}$ (<40 nmol/ml/min).
‡‡Normal, 8 to 52 U/liter.

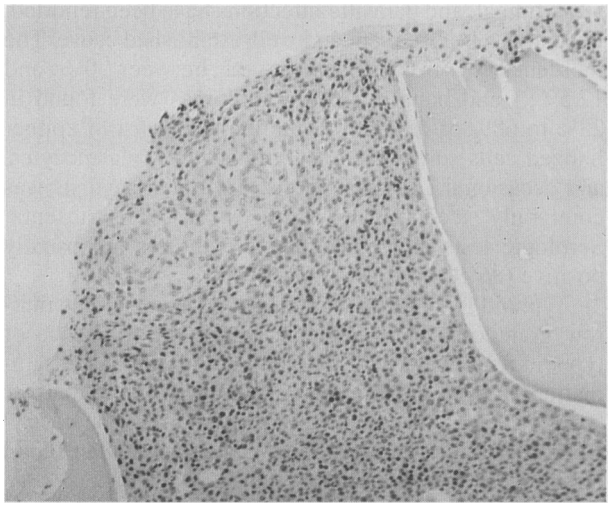

Figure 1.—A section of the bone marrow shows granuloma (hematoxylin and eosin stain, original magnification ×10).

and two had the classical finding for Q fever: the "donut" lesion (or fibrin-ring granuloma) that consists of a central empty space (probably an adipocyte), surrounded by lymphocytes and a characteristic fibrin ring. Serologic tests are usually positive.[21,22] Fibrin-ring granulomas, once thought to be characteristic of Q fever, can be seen in patients with Hodgkin's disease,[23,24] cytomegalovirus (CMV),[25] Epstein-Barr virus (EBV) infection,[26] hepatitis A,[27] giant cell arteritis,[23] leishmaniasis,[28] and allopurinol hepatitis.[24,29]

Tuberculosis is one of the most frequent causes of bone marrow granuloma; it constitutes 6% to 48% of the cases.[1-5] In cases of miliary tuberculosis, 33% to 100% of bone marrow biopsies will show granulomas. Yet, caseating necrosis is uncommon (29%), and the presence of AFB by the Ziehl-Neelsen stain is rare.[30] Marrow patchy necrosis can be seen. The lowest recovery of organisms by culture was from the bone marrow—15% compared with 78% from the sputum.[5] In patients with the acquired immunodeficiency syndrome (AIDS) with diagnosed disseminated tuberculosis and bone marrow granulomas, cultures of the bone marrow were positive in less than 50% of the cases.[31]

In a review of 13 patients with disseminated *Mycobacterium avium-intracellulare* who had a bone marrow biopsy, 9 (69) had a bone marrow granuloma.[32] No necrosis or caseation was found in any of the granulomas. Staining for AFB was positive in only one case. Cultures for *M avium-intracellulare* were positive in 7 of the patients.[32]

Bone marrow granulomas have been described in the marrow of patients with disseminated bacillus Calmette-Guérin infection following vaccination.[33,34] The granulomas were noted to be noncaseating in all four patients who had a bone marrow biopsy.[34]

Disseminated fungal infections rank high on the differential diagnosis of bone marrow granuloma. With the spread of HIV, it is expected that the incidence of these diseases will rise, with histoplasmosis being the leading cause. The incidence of histoplasmosis varied among the different studies. In contrast to a Spanish study in which an incidence of 0% was found,[4] the study by Boden showed an incidence of 20%.[2] This finding might be due to epidemiologic factors. In immunocompromised patients, the chances of dissemination to the bone marrow are high. In a study of 58 immunocompromised patients infected with histoplasmosis, 33 had histoplasmosis in the bone marrow.[35] Bone marrow was the best specimen from which to recover the organism.[35] In another study, 8 of 18 patients with proven histoplasmosis had a typical granuloma in the bone marrow. The organism was found in 7 patients with the silver-methenamine stain. The organisms were rare and hard to find. There was no evidence of caseating necrosis. Epithelioid cells and some giant cells were found.[36]

Epstein-Barr virus and CMV are the most frequently reported viruses to cause bone marrow granuloma. The incidence of bone marrow granuloma from EBV was about 10% in one study.[3] In a 1950 review of 23 cases of mononucleosis with bone marrow biopsies, granulomas were found in 11 of the patients (48%).[37] No characteristics were identified. Other isolated reports have associated EBV with bone marrow granuloma.[38,39] It is possible that some cases diagnosed as "mononucleosis" before the use of serologic markers are in fact due to CMV infections. With the introduction of more specific testing techniques, CMV is being recognized as a cause of bone marrow granuloma.[40]

Bone marrow granuloma is a common finding in patients with AIDS. Most of them are due to disseminated mycobacterial or fungal infections. In a study of 342 bone marrow biopsy specimens from patients with AIDS, 30% had a granuloma: 80% were related to infectious diseases, and 64% were due to mycobacterial or fungal infections. Interestingly, 20% were of undetermined cause.[31] The granulomas were subtle, small, loosely cohesive, and difficult to detect.[31] In another

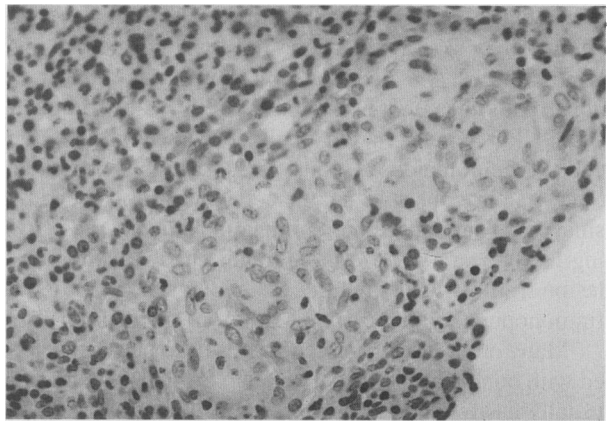

Figure 2.—An enlargement of a section of bone marrow shows giant cells (hematoxylin and eosin stain, original magnification ×40).

TABLE 2.—*Distribution of the Causes of Bone Marrow Granulomas in 5 Major Series of Bone Marrow Biopsies**

Cause	Series, No. of Cases (%)				
	Pease, 1956[3]	Bodem et al, 1983[2]	White and Johnston, 1985[5]	Vilalta-Castel et al, 1988[4]	Bharagrava and Farhi, 1988[1]
Mycobacteria	19 (22)	4 (7)	24 (48)	8 (20)	10 (12)
Histoplasmosis	6 (7)	11 (19)	--	0 (0)	3 (11)
Sarcoidosis	9 (10)	4 (7)	3 (6)	2 (5)	9 (11)
Lymphoma	15 (17)	8 (14)	7 (14)	4 (10)	15 (18)
CMV or EBV	16 (18)	2 (4)	--	0 (0)	3 (3)
Malignant neoplasm	--	4 (7)	2 (4)	3 (7.5)	14 (16)
Drugs	--	7 (12)	--	--	4 (5)
Autoimmune	2 (2)	5 (9)	--	1 (2.5)	2 (2)
Unknown	--	8 (13)	--	7 (17.5)	5 (6)
Total	87	58	50	40	72

CMV = cytomegalovirus, EBV = Epstein-Barr virus

*Not all the causes of bone marrow granuloma are given; therefore, the columns do not all add up to the total in each series.

study, 35 bone marrow biopsy specimens from 34 patients with AIDS showed granulomas in the bone marrow of 4 patients (1 was due to a *Mycobacterium* species, another to a foreign body, and 2 were of undetermined origin).[41]

Foreign bodies can be present in the bone marrow. Silicosis and coal workers' pneumoconiosis have been reported in association with bone marrow granuloma. In the case of coal workers, a characteristic yellow-brown pigment was found in the granuloma.[42,43] A foreign body granuloma was also described in the bone marrow of a patient with AIDS.[41]

Isolated reports have implicated many drugs in the genesis of bone marrow granulomas. In all these cases, the granuloma was nonspecific. Usually in repeated biopsies, granulomas have been reported to disappear or at least to diminish in number after the discontinuation of the drug.[43,44] The most commonly implicated drugs are procainamide and sulfonamide.[1,2]

Sarcoidosis is one of the most frequent causes of bone marrow granuloma. It is rare for sarcoidosis to present as a granuloma in bone marrow, and isolated extrapulmonary sarcoidosis occurs in less than 5% of cases. It is responsible for 3% to 32% of the cases of bone marrow granuloma, the average being around 10%.[1-5] In one study in which 17 patients with sarcoidosis underwent bone marrow biopsy, noncaseating granulomas were found in 9 of the patients (53%).[45] Lung involvement is present in 90% to 95% of cases. The diagnosis of sarcoid depends on clinical and radiologic findings, bronchoalveolar lavage, and ACE levels. Angiotensin-converting enzyme levels have been substantially higher in patients with sarcoidosis than in those with other pulmonary diseases, but this is a nonspecific finding and should not be regarded as pathognomonic of sarcoidosis.[46-48] Most of the granulomas did not show characteristic features.[48]

Some connective tissue diseases have been associated with bone marrow granuloma. Most reports are of isolated cases.[3,4]

Finally, as many as 13% of the cases of bone marrow granuloma are of undetermined origin. In one report, a syndrome consisting of diffuse granulomatosis (affecting spleen, liver and bone marrow) with fever of unknown origin was described that responded to the administration of steroids.[49] Of 20 patients, 5 had a definitive diagnosis after long-term follow-up, but 15 remained "idiopathic." The controversy still exists whether these patients had sarcoidosis without lung involvement or a completely different disorder. Steroid therapy improved the outcome in all 15 patients.[49]

In summary, the histologic finding of a bone marrow granuloma, although rarely pathognomonic, points toward a well-known spectrum of diseases. Consideration of the clinical data and communication between the pathologist and primary care physician should help clarify the cause.

In general, strong consideration is warranted for a purified-protein derivative skin test, a sputum and bone marrow culture for AFB, a direct AFB stain, culture for fungus, and a chest x-ray film. A serologic test should be done for *H capsulatum* in areas of high prevalence, and the biopsy specimen should be carefully inspected for AFB and fungus under adequate stains. The treatment of tuberculosis should be considered until cultures are negative after six to eight weeks. Serologic testing for HIV is indicated if the diagnosis of disseminated tuberculosis, histoplasmosis, or *M avium intracellulare* is made or the patient belongs to a high-risk group.

The search for lymphoma should be thorough. Immunophenotyping of the bone marrow could be helpful. The finding of a bone marrow granuloma in patients with lymphomas must be assessed carefully because such patients are often immunocompromised and prone to the development of systemic infections with tuberculosis, histoplasmosis, CMV, and other opportunistic infections. A search for brucellosis, typhoid fever, and Q fever should depend on clinical findings. A high ACE level supports the diagnosis of sarcoidosis but is not specific.

TABLE 3.—*Differential Diagnosis of Bone Marrow Granulomas*

Malignant neoplasms
Hodgkin's disease
Non-Hodgkin's lymphoma
Acute lymphocytic leukemia*
Acute myelocytic/myelogenous leukemia*
Chronic myelocytic/myelogenous leukemia*
Multiple myeloma*
Malignant histiocytosis*
Refractory anemia with excess blasts*
Colon carcinoma*
Lung carcinoma*
Ovarian carcinoma*
Neuroblastoma*
Sarcoma*

Infectious causes
Brucellosis
Typhoid fever
Q fever
Tularemia*
Mycoplasma species*
Tuberculosis
Mycobacterium avium-intracellulare
Bacillus Calmette-Guérin*
Leprosy*
Rickettsiosis*
Syphilis*
Histoplasmosis
Cryptococcosis*
Coccidioidomycosis*
Aspergillosis*
Blastomycosis*
Epstein-Barr virus
Cytomegalovirus
Human immunodeficiency virus
Hepatitis C virus*
Herpesvirus*

Drugs
Procainamide
Sulfonamide
Chlorpropamide*
Phenylbutazone*
Phenytoin*
Methyldopa*
Allopurinol*
Ibuprofen*
Penicillamine*
Tolmetin sodium*

Foreign bodies

Connective tissue diseases
Rheumatoid arthritis*
Felty's syndrome*
Primary biliary cirrhosis*
Sjögren's disease*
Pulmonary fibrosis*
Systemic lupus erythematosus*
Addison's disease*
Behçet's disease*
Erythema nodosum*
Temporal arteritis*
Hemolytic anemia*
Chronic renal failure

Sarcoidosis

Idiopathic diffuse granulomatosis

*These items are rare causes.

Drugs taken by patients should be reviewed, and those susceptible of causing a granuloma should be withdrawn if possible. The disappearance of granuloma on a later biopsy supports the diagnosis of drug-induced bone marrow granuloma.

Autoimmune diseases and other systemic diseases should be considered, depending on the clinical presentation and after the other more frequent causes of bone marrow granulomas have been ruled out. Finally, the diagnosis of idiopathic granulomatosis is a diagnosis of exclusion. Treatment with steroids has been shown to be beneficial in patients with this disorder.

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